REMARKS

Applicants acknowledge with appreciation the time and courtesies extended by the examiner toward applicants' representative during a telephone interview conducted with applicants' representative on Tuesday, November 1, 2005. The examiner's insights and comments have advanced the prosecution of the case. In particular, the outstanding 35 U.S.C. §103(a) rejections, and more specifically the cited references. Further discussion involved potential claim amendments and ways this matter can move forward.

Applicants address the examiner's remarks in the order presented in the Office Action (dated July 5, 2005). All claim amendments are made without prejudice and do not represent acquiescence in any ground of rejection.

STATUS OF THE CLAIMS

Claims 13, 18, and 19 are currently pending. Claim 13 is amended. After entry of this amendment, Claims 13, 18, and 19 will be pending. Support for the amendments to claim 13 can be found in the claims as originally filed and throughout the application as filed. Additional support for "whereby the training data set is generated from a genotype-phenotype database" can be found, for example, at page 7, lines 29-30; page 18, lines 9-21.

Claims 13, 18, and 19 remain rejected under 35 U.S.C. §103(a) as being unpatentable over Ioannidis *et al.*, 1998, *American Journal of Epidemiology* 147: 464-471, in view of Harrigan *et al.*, 1999, *AIDS* 13: 1863-1871, for the reasons stated in the previous Office Action.

REJECTIONS UNDER 35 U.S.C. §103(A)

Claims 13, 18, and 19 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ioannidis *et al.*, 1998, *American Journal of Epidemiology* 147: 464-471, in view of Harrigan *et al.*, 1999, *AIDS* 13: 1863-1871. Applicants have amended claim 13 for greater clarity and consistency of claims language. Applicants also respectfully traverse in part.

According to the examiner, the instant claims are drawn to a neural network for predicting resistance of HIV to a therapeutic agent. The examiner characterizes Ioannidis *et al.* as teaching the use of neural networks in modeling complex immunogenetic associations of disease. In particular, the examiner stated that Ioannidis *et al.* teach a feed-forward neural network with back propagation (claim 1), including a training process where weights are adjusted to minimize error (page 465, column 2). The examiner further states that the network is composed of several layers of neurons, including an input layer, one or more hidden layers, and an output layer (claims 18 and 19).

While Ioannidis *et al.* do teach the use of a neural network for allele prediction in AIDS, the examiner notes that Ioannidis *et al.* do not specifically teach the prediction of resistance of HIV to a therapeutic agent. For this purpose, the examiner uses Harrigan *et al.* as teaching drug resistance determination.

According to the examiner, Harrigan *et al.* teach phenotype and genotype assessment of resistance of 10 different antiviral agents. This baseline drug resistance method was predictive of resistance of HIV to ritonavir and saquinavir. Drug resistance phenotype was predictive of poor virological response to this particular dual protease inhibitor combination (page 1863). The examiner states that the conclusion drawn was that baseline resistance to

ritonavir or saquinavir or both was associated with poor antiviral response. The data suggest, according to the authors, that the measurement of drug resistance *may* assist in optimizing antiretroviral therapy in the clinic (page 1863) (emphasis added by applicants). Therefore, the examiner takes the position that it would have been *prima facie* obvious to one of skill in the art at the time of the invention to employ the neural network of Ioannidis *et al.* for the assessment of predicting drug resistance of HIV, as allegedly is characterized to have been done by Harrigan *et al.*

Specifically the examiner points to the motivation to use a neural network is provided in the statement by Ioannidis *et al.*, which says, "neural networks could be trained to recognize genetic patterns in conjunction with associated clinical outcomes, and their performance in modeling these complex associations in a training set was superior to logistic regression models." (page 469, column 1). According to the examiner, Harrigan *et al.* use logistic regression in their assessment of baseline resistance; however, it would have been obvious to improve the accuracy of the resistance testing by using the neural network of Ioannidis *et al.* for the reasons set forth above. Applicants traverse for the following reasons.

As Applicant has noted previously, establishment of a *prima facie* case of obviousness requires the following elements. First, the claimed invention must be considered as a whole, and all limitations of the claims must be taken into account. Second, the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the modification or combination. In addition, the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention. Finally, a reasonable expectation of success is the standard with which obviousness is determined.

Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986); MPEP §2141.

No motivation to combine Ioannidis *et al.* with Harrigan *et al.* has been established on this record. The importance of the requirement of a motivation to combine prior art references has been explained by the Federal Circuit as follows:

> When patentability turns on the question of obviousness, the search for and analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness.... "The factual inquiry whether to combine references must be thorough and searching." It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with.

In re Lee, 277 F.3d 1338 (Fed. Cir. 2002) (citations omitted). The teaching or suggestion supporting the desirability of the combination may not be based on the applicant's disclosure. *See In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992). Furthermore, the examiner is prohibited from basing an obviousness rejection on hindsight reconstruction using the application as a blueprint. *See In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to depreciate the claimed invention.").

In a previous reply, Applicant has argued that the aforementioned requirements for obviousness have not been met by the cited references, alone or in combination.

Ioannidis *et al.* is considered to constitute the closest prior art, because it employs neural networks to correlate immunogenetic markers with AIDS disease progression.

Ioannidis *et al.* employ: as input: human leukocyte antigen (HLA) data on class I and class II alleles and TAP variants for the training and validation of the neural network; and as output: a binary outcome - one or zero, for the progression to AIDS within 6 years or not.

The objective problem which the current invention seeks to solve is the provision of a computational tool that can recognize complex genetic patterns of resistance within the therapy dimension, *i.e.*, individual and combination of base mutations, which confer resistance, cross-resistance, susceptibility and cross-susceptibility to one or more of the antivirals or other therapeutic agents available in the market. This problem is now solved by the invention as addressed in claim 13.

The difference of claim 13 with Ioannidis *et al.* is the training data set, the testing data set and the query inputs and outputs which correspond to one or more genetic mutations (input) and their paired phenotypic resistance change (output).

The teaching disclosed by Harrigan *et al.* makes actual correlations of genotypes and/or phenotypes with clinical response, expressed in logarithmic viral load values (copies of RNA per mL). To achieve this correlation, Harrigan *et al.* employ a univariate and multivariate logistic regression. The approach by Harrigan *et al.* is further limited in that it predicts clinical response on the administration of ritonavir and saquinavir only, which are both protease inhibitors. Conversely, the present invention is able to predict resistance (***not*** clinical response as taught by Harrigan *et al.* and discussed in further detail below) to any antiviral compound or therapeutic agent, be it a protease inhibitor, a reverse-transcriptase inhibitor, an entry inhibitor, and the like, or any combination thereof. Accordingly, the skilled artisan would have no reasonable expectation that such a modification of Ioannidis *et al.* using the teaching of Harrigan *et al.* would be successful.

Harrigan *et al.* teach correlating genotypic and/or phenotypic resistance with clinical resistance. Ioannidis *et al.*, on the other hand, correlates HLA genotypic sequences with clinical resistance, expressed as 0 (no disease progression to AIDS within 6 years) or 1

(disease progression to AIDS within 6 years). Both Harrigan and Ioannidis disclose physical assays.

Applicants' instant invention, conversely, correlates genotypic resistance with phenotypic resistance. Taking an HIV sequence (*e.g.*, ACTG.....) as input, it is able to calculate an IC_{50} value against one or more antivirals or other therapeutic agents. See, *e.g.*, Table 7 in the instant specification. Applicants' invention is more akin to a computational or bioinformatics tool rather than a physical assay system.

Even if Ioannidis *et al.* were to be combined with Harrigan *et al.*, one of skill in the art would not arrive at the subject matter as claimed in claim 13 or disclosed in the instant specification. Both prior art documents, while employing different approaches (neural networks and logistic regression respectively), are both focused on correlating genotypic and/or phenotypic (in the case of Harrigan *et al.*) markers with clinical outcomes, be it disease progression or viral load changes.

On the provision of a computational tool that can recognize complex genetic patterns of resistance within the drug dimension, both Ioannidis *et al.* and Harrigan *et al.* are completely silent and therefore the one of skill in the art would not be able to recognize the alleged technical problem starting from the disclosure of any one of the prior art documents.

Applicant continues to traverse this rejection for all of the reasons set forth above, and asserts for those reasons that the cited references do not support an obviousness rejection of the invention as claimed. To advance these claims to allowance, however, and without intending to acquiesce to the correctness of the examiner's position, Applicant submits amended claim 13. More specifically, applicants have amended the training data set in claim 13 as being generated from a genotype-phenotype database. By employing bioinformatics

tools to genotyping and phenotyping methodologies, applicants' invention accurately predicts resistance of patient's pathogen or malignant cells to a therapeutic agent based on genotypic mutaions in the pathogen or malignant cell. A phenotype-genotype database is generated to correlate each of the known genotype mutations with changes in the phenotypic drug resistance of that pathogen or malignant cell. By generating such a database, the initial set-up time for the neural network is substantially reduced for the information from such databases are used to train and test the neural networks of the present invention.

Applicants' invention as claimed bridges the gap between the more meaningful data obtained from phenotypic testing and the more readily obtainable data obtained from genotypic testing through the use of a neural network.

Here, as in that case, there was no suggestion in the prior art itself as to the desirability of the modifying the teachings of one reference with those of the other. Additionally, neither reference specifically recognized or appreciated the advantages of Applicant's claims. Harrigan and Ioannidis are both silent with respect to a training data set that is generated from a genotype-phenotype database.

Furthermore, applicants submit that it is impermissible for the examiner to use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious. In re Fritch, 972 F.2d 1260, 23 USPQ.2d 1780 (Fed. Cir. 1992). The examiner cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. In re Fine, 837 F.2d 1071, 1075, 5 USPQ.2d 1596, 1600 (Fed. Cir. 1988). Applicants submit that the examiner is engaging in the impermissible hindsight construction of the applicants' claimed invention.

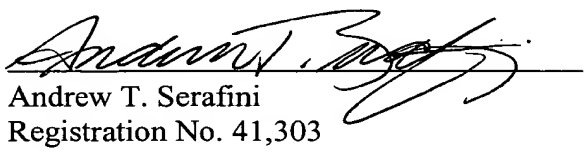
Applicants further assert that, even assuming that the requisite motivation to combine the selected elements of the cited references exists, which applicants deny, the ordinarily skilled artisan would have no reasonable expectation of success in arriving at the presently claimed methods and bacteria. At best, the Examiner's reasoning amounts only to an obviousness to try rationale; "obvious to try," however, is not the proper legal standard under 35 U.S.C. § 103. In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988).

Notwithstanding the foregoing, applicants have amended the claims to advance prosecution. Without acceding to the propriety of the rejection of pending claims 13, 18 and 19 under 35 U.S.C. § 103, applicants respectfully request reconsideration of the claims as amended. For these reasons, applicants request the examiner to withdraw the rejection of pending claims 13, 18, and 19 under 35 U.S.C. § 103.

The foregoing represents a *bona fide* attempt to advance the present case to allowance. Applicants submit that this application is now in condition for allowance.

Accordingly, an indication of allowability and an early Notice of Allowance are respectfully requested. If the examiner believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-332-1380.

Date: November 7, 2005



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